Hypertensive Renal Damage in Metabolic Syndrome Is Associated with Glucose Metabolism Disturbances

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Abstract. Recent evidence highlights the relationship between metabolic syndrome (MS) and increased risk of cardiovascular (CV) diseases. Mild renal function abnormalities are associated with an enhanced CV risk, considered to be due to the presence of associated risk factors. Hence, MS and renal abnormalities could be linked and contribute to augment CV risk. For estimating the prevalence of diminished creatinine clearance (CC; <60 ml/min per 1.73 m^2) in hypertensive patients with or without MS and for investigating the factors accompanying this abnormality, 1625 hypertensive patients, aged 18 yr or older, were included. The presence of MS was defined according to the Adult Treatment Panel III criteria. The overall prevalence of MS was 49.4% ($n = 802$). No significant difference was found for CC between those with and without MS, albeit the presence of MS was accompanied by greater urinary albumin excretion ($P = 0.01$). The prevalence of a diminished CC was also similar in the two groups. MS-positive patients presented a progressive decay in CC when classified as normoglycemic ($n = 319$), impaired fasting glucose ($n = 237$), and diabetic patients ($n = 246$; 85.9 ± 30.2, 81.8 ± 26.8, and 75.2 ± 25.7 ml/min per 1.73 m^2, respectively; $P = 0.0007$ linearity test) and the opposite for microalbuminuria (29.5 ± 45.5, 45.0 ± 96.6, and 74.1 ± 146.3 mg/24 h, respectively; $P = 0.001$ linearity test). In multiple regression analysis, factors related to the finding of a diminished CC in MS and non-MS patients were similar. Hypertensive patients at a relatively young age present with an elevated prevalence of minor abnormalities of renal function that is mostly related to the presence of metabolic alteration of glucose together with age and BP.

The prevalence of metabolic syndrome (MS) varies according to the population considered, ranging from 8.8 to 14.3% in Europe (1,2) to 22.6 to 23.7% in United States (3,4). In patients with MS, cardiovascular disease (CVD) and all-cause mortality are increased (5), even in the absence of baseline CVD and diabetes (1). After adjustment for conventional cardiovascular risk factors, men with MS are 2.9 times more likely to die of coronary heart disease (1). In addition, minor abnormalities of renal function (MRA; microalbuminuria, increased serum creatinine concentrations, decrease in estimated creatinine clearance (CC), or overt proteinuria) are also common and associated with a high prevalence of CVD (6). The association of MRA with the risk for adverse outcomes is strongly related to coexisting CVD and CVD risk factors (6–8). Recently, the National Kidney Foundation classified renal failure according to the levels of estimated GFR (9). An estimated GFR <60 ml/min (chronic kidney disease stage 3) has been identified as a predictor of elevated risk for CVD and death (6,10–12). There are few data relating the presence of MS to the presence of MRA. Therefore, our aims were (*1*) to determine the prevalence of MS in a cohort of hypertensive patients, (*2*) to analyze the prevalence of MRA in patients with MS, and (*3*) to detect possible factors that predict the finding of renal dysfunction in patients with MS.

Materials and Methods

Design

This is a cross-sectional study, intended to describe the prevalence of MS in a population of essential hypertensive patients who were attended to in a hospital-based hypertension unit, to define the clinical characteristics of hypertensive patients with MS, and to analyze the possible relationship between MS and MRA.

Definitions

Arterial hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg in the absence of medication or by the presence of antihypertensive therapy. MS was defined according to Adult Treatment Panel III (ATP-III) criteria (13). This definition requires that at least three of the following criteria be positive: waist circumference >102 cm in men and >88 cm in women, hypertriglyceridemia ≥150 mg/dl, HDL cholesterol <40 mg/dl in men and <50 mg/dl in women, BP ≥130/85 mmHg, and fasting glucose ≥110 mg/dl. Chronic renal failure was defined as a measured CC value <60 ml/min per 1.73 m^2. Microalbuminuria was defined as urinary albumin excretion 30 to 300 mg/24 h.

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Patients

We included 1625 essential hypertensive patients, men and women aged 18 yr or older, who were treated consecutively in our hypertension unit from September 2001 to September 2002. We collected complete clinical data (age, gender, weight, height, waist circumference, and BP), and blood sample and 24-h urine collection were obtained to measure serum values of creatinine, glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, serum uric acid, sodium and potassium, and CC and microalbuminuria.

Statistical Analyses

Results are expressed as means and SD or 95% confidence intervals as indicated. Statistical analyses were performed with the SPSS (version 10.0; SAS Institute, Cary, NC). The significance of the differences in categorical and continuous variables among groups was examined by means of the Pearson χ^2 test and *t* test, respectively. ANOVA test was used to analyze changes related to glycemic status in patients with MS. $P < 0.05$ was considered statistically significant. Cox regression analysis was performed, incorporating the most important predictors of renal outcome: age, baseline serum creatinine, BP values, serum glucose, smoking, and lipid profile.

Results

Prevalence of MS

The mean age of patients was 54.0 ± 14.6 yr (range, 18 to 85; 56.0% female). The overall prevalence of MS was 49.4% ($n = 802$) with no difference between genders (47.8% in men [$n = 715$] and 50.5% in women [$n = 910$]). As can be seen in Figure 1, the prevalence increased from 21.0% among patients aged 20 through 29 yr to 54.3% and 59.5% for patients aged 60 through 69 yr and 70 yr or older, respectively, the higher prevalence seen in young men and in old women.

As shown in Figure 2, the prevalence of each of the diagnostic criteria of MS varies with age. Notably, waist circumference and impaired fasting glucose but not hypertriglyceridemia nor low HDL cholesterol were strongly related to aging.

MS and non-MS patients showed clinical and biochemical differences, some of which were related to the definition of MS (BP, glycemia, lipid profile; Table 1). In comparison with non-MS patients, MS patients were older and showed higher levels of systolic, diastolic, and pulse pressure, higher serum levels of glucose and uric acid, and a more deranged lipid profile. There were no differences in renal parameters, except for microalbuminuria, which was higher in MS patients.

Prevalence of Renal Insufficiency

The overall prevalence of renal insufficiency was 21.5%, with no difference between MS and non-MS patients (20.2 and 22.8%, respectively). In patients with MS, the prevalence of renal insufficiency was 19.4, 21.5, and 28.5% for patients with fasting serum glucose levels that were normal ($n = 319$), impaired ($n = 237$), or within the diabetic range ($n = 246$), respectively ($P = 0.005$ for linear association). The prevalence of microalbuminuria was 24.7, 30.5, and 34.7% in MS patients with normoglycemia, impaired fasting glucose, or diabetes, respectively ($P = 0.000$ for linear association), which compares to 15.1% in normoglycemic non MS-patients. Table 2 shows clinical and biochemical characteristics of the three groups of MS patients classified according to fasting serum glucose levels.

No significant difference in CC was found in MS *versus* non-MS patients (81.4 ± 28.2 *versus* 83.6 ± 28 ml/min per 1.73 m^2, respectively), although MS patients had a greater urinary albumin excretion (49.2 ± 105 *versus* 32.6 ± 82 mg/24 h; $P = 0.01$). Normoglycemic non-MS and normoglycemic MS patients exhibited comparable levels of CC (84.9 ± 28.5

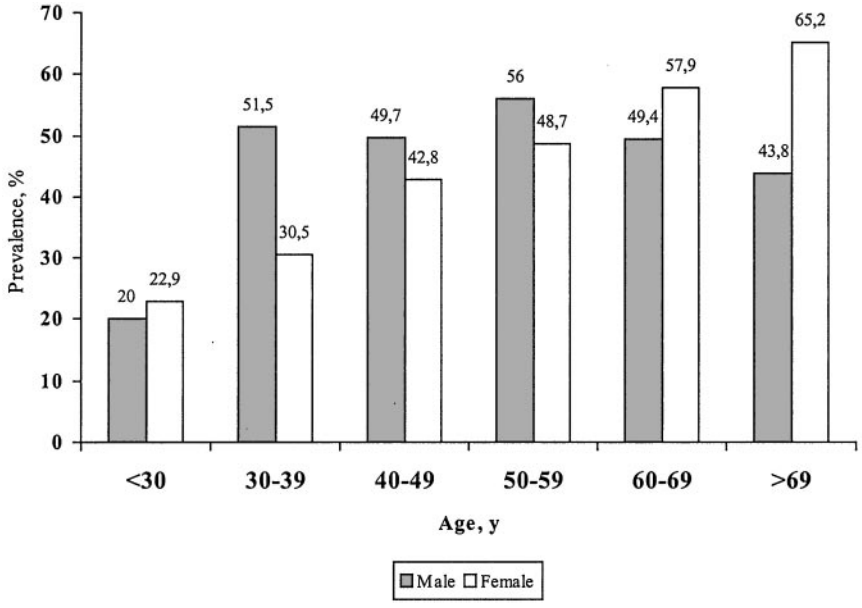

Figure 1. Age-specific prevalence of the metabolic syndrome (MS) in a cohort of hypertensive patients.

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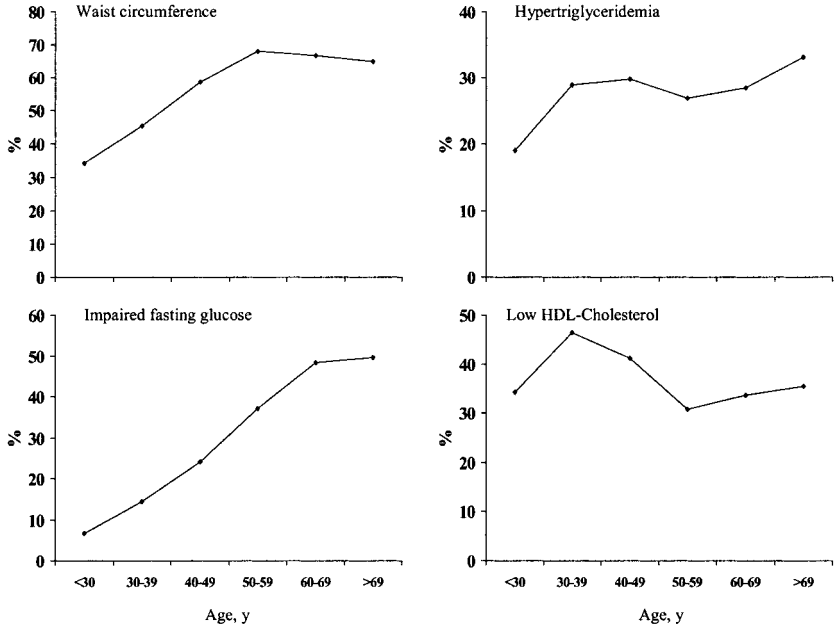

Figure 2. Age-specific prevalence of the diagnostic criteria of MS.

Table 1. Clinical and biochemical differences in MS and non-MS patients

	Non-MS	MS	*P*
N	823	802	
Age (yr)	51.4 ± 15.5	56.7 ± 13.3	0.000
Smoking (%)	9.3	8.8	0.223
BMI (kg/m^2)	27.3 ± 4.4	31.6 ± 4.5	0.000
SBP (mmHg)	150.8 ± 22.0	150.8 ± 22.7	0.000
DBP (mmHg)	91.6 ± 11.6	93.6 ± 11.9	0.001
PP (mmHg)	59.2 ± 17.7	64.4 ± 18.9	0.000
Glycemia (mg/dl)	99.9 ± 16.7	125.5 ± 40.7	0.000
Total cholesterol (mg/dl)	217.5 ± 37.7	229.2 ± 41.3	0.000
Triglycerides (mg/dl)	100.4 ± 39.4	161.8 ± 79.7	0.000
HDL cholesterol (mg/dl)	56.1 ± 12.0	45.5 ± 11.4	0.000
LDL cholesterol (mg/dl)	142.0 ± 34.1	152.4 ± 35.5	0.000
Serum creatinine (mg/dl)	1.01 ± 0.3	1.02 ± 0.3	0.297
Creatinine clearance (ml/min per 1.73 m^2)	83.6 ± 28.1	81.4 ± 28.2	0.121
Microalbuminuria (mg/24 h)	32.7 ± 81.9	49.1 ± 105.1	0.010
Serum uric acid (mg/dl)	5.5 ± 1.7	6.2 ± 1.8	0.000

MS, metabolic syndrome; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure.

versus 85.9 ± 30.2 ml/min per 1.73 m^2, respectively; $P = 0.631$) and microalbuminuria (31.1 ± 82.6 *versus* 29.5 ± 45.5 mg/24 h, respectively; $P = 0.817$; Figure 3). However, considering the three intervals of fasting serum glucose as a continuum, a significant negative trend was found for CC values, moving from 85.9 ± 30.2 to 81.8 ± 26.8 and to 75.2 ± 25.7 ml/min per 1.73 m^2 for normal fasting glucose, impaired fasting glucose, and diabetes, respectively ($P = 0.000$ linearity test). A similar but positive trend was observed for microalbuminuria that rose from 29.5 ± 45.5 to 45.0 ± 96.6 and to 74.1 ± 146.3 mg/24 h, respectively ($P = 0.001$ linearity test; Figure 3).

Factors Related to the Development of Renal Dysfunction in MS

In multiple regression analysis, including the most important predictors of renal outcome (age, serum creatinine, BP values, serum glucose, lipid profile, and smoking), only age and serum glucose were independent factors related to CC in MS patients. Similarly, serum glucose was the only independent predictor of microalbuminuria (Table 3).

For the sake of comparison, a similar analysis was performed in patients without MS ($n = 823$) in whom a similar prevalence of diminished CC was observed. The predictors of a diminished CC were age (hazard ratio [HR], 2.04; 95% confidence interval [CI],

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Table 2. Clinical and biochemical differences related with glycemic status in MS patients

	Normoglycemia	Impaired Fasting Glucose	Diabetes	*P* (trend)
N	319	237	246	
Age (yr)	52.0 ± 14.2	57.5 ± 11.9	61.9 ± 10.9	0.000
BMI (kg/m^2)	31.54 ± 4.33	31.55 ± 4.40	31.77 ± 4.91	0.806
SBP (mmHg)	152 ± 22	160 ± 21	164 ± 23	0.000
DBP (mmHg)	93 ± 12	94 ± 12	94 ± 12	0.754
PP (mmHg)	59 ± 18	66 ± 18	70 ± 20	0.000
Glycemia (mg/dl)	97.4 ± 7.4	115.9 ± 4.6	171.1 ± 46.0	0.000
Creatinine (mg/dl)	1.00 ± 0.25	1.05 ± 0.27	1.02 ± 0.25	0.057
Creatinine clearance (ml/min per 1.73 m^2)	85.9 ± 30.2	81.8 ± 26.8	75.2 ± 25.7	0.000
Microalbuminuria (mg/24 h)	29.5 ± 45.5	45.0 ± 96.6	74.1 ± 146.3	0.001
Serum uric acid (mg/dl)	6.0 ± 1.8	6.4 ± 1.7	6.3 ± 1.7	0.058

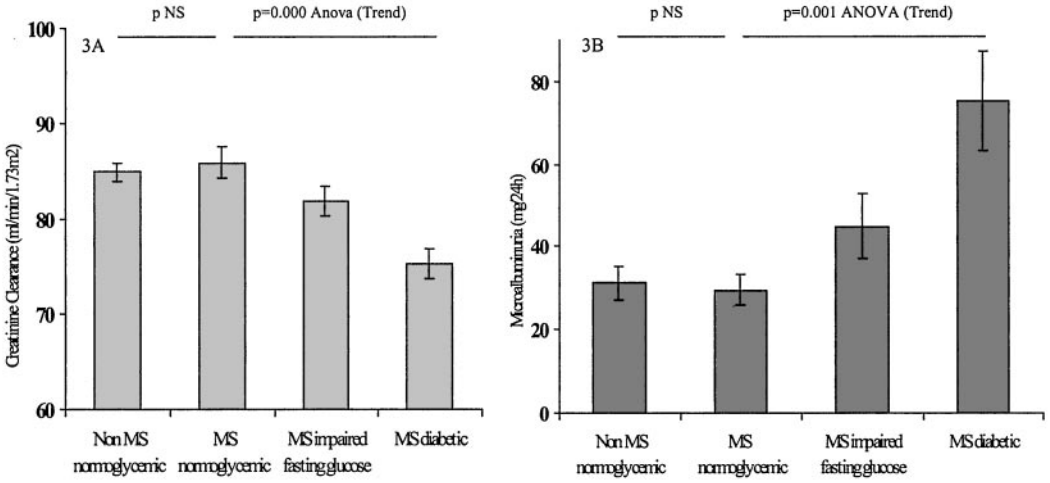

Figure 3. (A) Non-MS normoglycemic and MS normoglycemic patients show similar values of creatinine clearance. In MS patients, creatinine clearance decreases progressively according glycemic status. (B) Non-MS normoglycemic and MS normoglycemic patients show similar values of urinary albumin excretion. In MS patients, urinary albumin excretion increases progressively according glycemic status.

Table 3. Multiple regression analysis

	HR	95% CI	*P*
Independent predictors of creatinine clearance in patients with MS			
Age	1.91	1.66–2.20	0.000
Glycemia	1.08	1.03–1.13	0.001
Independent predictor of microalbuminuria in patients with MS			
Glycemia	1.71	1.37–2.14	0.000

Hazard ratios for age and glycemia are 1 yr and 1 mg/dl increases, respectively. Variables excluded from the initial model are as follows: age, gender, smoking, BMI, BP values, and lipid profile.

1.81 to 2.30; $P = 0.000$), body mass index (HR, 1.71; 95% CI, 1.13 to 2.58; $P = 0.011$), and fasting serum glucose (HR, 1.18; 95% CI, 1.00 to 1.25; $P = 0.046$). In these patients, systolic BP was the most important predictor of microalbuminuria (HR, 1.53; 95% CI, 1.09 to 2.16; $P = 0.015$).

Discussion

Our results confirm previous reports of a prevalence of MS in hypertensive patients clearly above that observed in the general population (1–4). The result is important because the presence of MS identifies subjects with increased cardiovascular morbidity and mortality (5), characterized by an increased risk of coronary heart disease (1,14), adverse changes in peripheral arteries (15), and increased risk of progressive carotid atherosclerosis (16). Patients with MS show an elevated percentage of intermediate signs of target organ damage, such as the increase of left ventricular mass (17) and the presence of microalbuminuria as a marker of endothelial dysfunction (18). Furthermore, it has been described that hyperinsulinism and an increased insulin resistance are the main pathophysiologic features of MS. These metabolic disorders precede the development of diabetes (19), and they can be early manifestations of atherosclerotic damage (20).

In recent years, the importance of MRA as a predictor of cardiovascular morbidity and mortality has been amply recog-

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nized (6). In fact, 3% of the general population in the United States present with a serum creatinine >1.6 mg/dl in men or 1.4 mg/dl in women (21), 9.3% present with micro-macroalbuminuria (22), and 7.7% present with a diminished estimated GFR (23). It has been shown that the main reason for the increased CV risk accompanying MRA is the presence of several other associated risk factors, such as insulin resistance (19), oxidative stress (24), proinflammatory markers (8), left ventricular hypertrophy (7), and so forth. In consequence, it is likely that most of the patients who present with a diminished CC would be included in the group presenting with MS. The relevance of the finding of a diminished estimated GFR or measured CC has been clearly established in population-based studies (10), as well as in essential hypertensive patients (25). In fact, the latest hypertension guidelines recognized this alteration, along with the other minor abnormalities of renal function, as an associated risk factor in hypertensive patients (26).

Our series of patients followed in a hospital-based hypertension unit shows that almost one in four patients at a mean age of 54 yr presents with a diminished CC. To our surprise, patients with and without MS, according to the ATP-III criteria (13), showed a similar percentage of diminished CC. The two groups differed significantly in their clinical and biochemical characteristics, in particular, age, body mass index, BP levels, fasting serum glucose, and serum uric acid, all of which were higher in MS patients than in non-MS patients. They also presented a more deranged lipid profile, but serum creatinine and CC values were similar. According to these data, it could be speculated that the full expression of MS will occur a few years later in many of the non-MS patients. Also, it could be argued that the similar levels of CC in MS patients, when compared with non-MS patients at older ages, suggest the existence of hyperfiltration as a possible marker of early target organ damage (27).

The multivariate analysis disclosed that in the presence of MS, glucose metabolism disturbance and age were the main findings related to the presence of a diminished CC. Meanwhile, only glucose disturbances were related to microalbuminuria. These results are in agreement with previously published data by Redon *et al.* (28), who described that systolic BP and fasting glucose were the most relevant predictors of the development of microalbuminuria. Recent studies suggest that a mild alteration in glucose metabolism may be a major determinant of the age-associated decline in renal perfusion and glomerular filtration (29). Experimental data suggest that, before the development of glucose intolerance or hypertension, high glucose intake impairs renal function (30). Smoking has been considered a relevant risk factor for the development and progression of renal failure (31). In our series, the percentage of smokers was small, and probably for this reason, tobacco was not found to be related to diminished CC.

A similar analysis performed in non-MS patients revealed that the finding of diminished CC was significantly related to age, fasting serum glucose, and body weight, and, in the case of microalbuminuria, the significantly related factors were systolic BP and gender. These results favor the thesis that, among patients not classifiable as having MS, according to the ATP-III, the parameters related to a diminished CC resemble those seen among patients with MS. Some degree of overlapping between the two groups of patients must then exist, considering the mechanisms underlying renal damage, explaining the similar prevalence of diminished CC in patients with and without MS.

In summary, hypertensive patients at a relatively young age present with an elevated prevalence of MRA that is mostly related to the presence of metabolic alteration of glucose together with age and BP.

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